



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/CA98/00660 <b>(22) International Filing Date:</b> 8 July 1998 (08.07.98) <b>(30) Priority Data:</b> 2,208,924                      9 July 1997 (09.07.97)                      CA <b>(71) Applicant (for all designated States except US):</b> HYAL PHARMACEUTICAL CORPORATION [CA/CA]; 2425 Skymark Avenue, Mississauga, Ontario L4W 4Y6 (CA). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> ASCULAI, Samuel, S. [US/CA]; 2425 Skymark Avenue, Mississauga, Ontario L4W 4Y6 (CA). MOORE, Adrian [GB/GB]; The Medical College of Saint Bartholomew's Hospital, Dept. of Experimental Pathology, Charterhouse Square, London EC1M 6BQ (GB). <b>(74) Agent:</b> HUGHES, ETIGSON; Suite 200, 175 Commerce Valley Drive West, Thornhill, Ontario L3T 7P6 (CA).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> PACLITAXEL COMPOSITIONS CONTAINING HYALURONIC ACID OF A MOLECULAR WEIGHT OF LESS THAN 750.000 DA		
<b>(57) Abstract</b>  This invention relates to the use of forms of hyaluronan for use to deliver effective dosage amounts of the agent paclitaxel sold under the trade mark "Taxol" <sup>TM</sup> to a patient which medicine is present in a dosage amount much less than the usual amount presently being used when treating a patient with cancer.		

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PACLITAXEL COMPOSITIONS CONTAINING HYALURONIC ACID OF A MOLECULAR WEIGHT OF LESS THAN 750.000 DA

### **FIELD OF INVENTION**

5 This invention relates to the use of forms of hyaluronan for use to deliver to a patient the highly lipophilic therapeutic compound paclitaxel for example sold under the trade mark Taxol and in one aspect, to deliver effective dosage amounts of paclitaxel to the patient in need thereof which amount of paclitaxel is present in an effective dosage amount which is less than the usual dosage amount used today when treating a patient having cancer. In one aspect, this invention relates to the use of forms of  
10 hyaluronan to deliver amounts of the highly lipophilic therapeutic compound paclitaxel in such amount which would today not be normally expected to provide effective treatment to a patient and which amount becomes effective for treating the patient when combined with a form of hyaluronan.  
15

### **BACKGROUND OF INVENTION**

PCT Application No. WO 91/04058 discloses the use of forms of hyaluronan for delivery of medicines and therapeutic agents for the treatment of diseases and conditions of patients. The treatments were for underperfused tissue and pathological tissue (see p. 24 of the PCT Application).  
20

Among the medicines and therapeutic agents suitable for delivery by hyaluronan are lipophilic therapeutic compounds such as chemotherapeutic agents to treat the underperfused and pathological  
25 tissue including tumours. While the usual dosage amounts known at the time of application WO 91/04058 of the agent are successfully administered by the use of hyaluronan, larger dosage amounts (excess amounts) of medicines (such as NSAIDS) may also be successfully used to treat patients without the usual deleterious side effects expected. The amount of hyaluronan substantially reduces the significant deleterious  
30 side effects of for example the NSAIDS when administered together even when substantially larger dosage amounts of NSAIDS are used.

### **SUMMARY OF INVENTION**

Applicants have now discovered that substantially lesser amounts  
35 than the usual dosage amounts of the highly lipophilic therapeutic compound paclitaxel may be successfully administered to treat patients and such lesser amounts will be effective dosage amounts in the treatment if administered with a form of hyaluronan to treat

underperfused tissue and/or pathological tissue (which express excess hyaluronan receptors [more than normal tissue]) such as tumours. This unexpected finding provides the benefit to the patient of successful treatment of pathological tissue expressing excess hyaluronan receptors, while receiving much less than the usual accepted dosage amount of the highly lipophilic agent paclitaxel. As paclitaxel is toxic, the patient is not administered as much as previously. The toxic side-effects of paclitaxel on the patient and particularly his/her liver is very much reduced. Additionally as paclitaxel is expensive (in the order of about \$14,000/kg. of Taxol™) and the usual dosage of 175mg/m<sup>2</sup> administered intravenously over 3 hours every three weeks is reduced substantially, the costs of treatment are substantially reduced. Thus, paclitaxel for example paclitaxel diphenhydromine is "spared" (the amount being used in one dosage is substantially reduced from that normally used by itself).

It is therefore an object of this invention to provide improved formulations comprising "spared" amounts of the highly lipophilic antineoplastic agent paclitaxel for the treatment of cancer.

It is a further object of the invention to provide methods of treatment of patients using the spared amounts of the agent paclitaxel in dosage amounts of formulations comprising forms of hyaluronan and which spared amounts of the agent are effective amounts for successful treatment of patients having for example cancer when administered with forms of hyaluronan and which amount of the agent paclitaxel would not otherwise be an effective amount if administered without hyaluronan. Such spared amounts of the medicine paclitaxel may be as much as about 4 - 6 times less than the usual amount of paclitaxel administered alone and still be effective when combined with hyaluronan. For example, where Taxol™ (paclitaxel) is involved, the amount of Taxol™ (paclitaxel) "spared" may be at least 3 times less (and as much as 4 - 6 times less) than the usual dosage amount of the agent when administered without hyaluronan.

The accepted amount of paclitaxel usually given to a patient is in the order of 175mg/m<sup>2</sup>. In accordance with this invention, an effective amount of paclitaxel sold under the trade mark Taxol™ may be in the order of 55mg/m<sup>2</sup> or less (such as 28mg/m<sup>2</sup>) when paclitaxel is administered with the form of hyaluronan and such amount is now found to be effective in the treatment of patients suffering from cancer.

The form of hyaluronan may comprise amounts between 10mg and 1000mg or more in each dosage amount. As hyaluronan is not toxic, even greater amounts of hyaluronan may be used in each dosage for example up to 3000mg per dosage.

5 The dosages are administered to a patient as required - for example, dosages per week for the duration of treatment. The dosages may be administered by injection, intravenously or directly into the tumour.

The form of hyaluronan may be selected from hyaluronan and pharmaceutically acceptable non-toxic salts thereof such as sodium  
10 hyaluronate.

Many forms of hyaluronan may be suitable for use herein although those preferred are those discussed hereafter. Molecular weights of forms of hyaluronan less than about 750,000 daltons and preferably greater than 150,000 daltons (protein standard) in sterile water prepared having a  
15 viscosity for intravenous administration are suitable.

One specific form of pharmaceutical grade is a 1% sterile sodium hyaluronate solution (50 ml vials) provided by Hyal Pharmaceutical Corporation which has the following characteristics:

<u>Tests</u>	<u>Specifications</u>
20 1. Container Description	1 50 mL Flint glass vial with a red or gray rubber stopper and an aluminum seal, 20 mm in size.
25 2. Product Description	A clear, colourless, odourless, transparent, slightly viscous liquid.
3. Fill Volume	50.0 to 52.0 mL
4. pH	5.0 to 7.0 at 25 degrees C.
5. Specific Gravity	0.990 to 1.010 at 25 degrees C.
30 6. Intrinsic Viscosity	4.5 to 11.0 dL/g
7. Molecular Weight	178,000 to 562,000 daltons
8. Sodium Hyaluronate Assay and Identification	9.0 to 11.0 mg/mL. Positive
9. Particulate Matter	No visible Particulate Matter
35 10. Sterility	Meets Requirements for Sterility, USP 23
11. Bacterial Endotoxins (LAL)	Meets Requirements for Bacterial Endotoxins, USP 23.

This pharmaceutical grade 1% sterile solution of hyaluronan may be made from granules/powder having the following characteristics:

<u>Tests</u>	<u>Specifications</u>
1. Description	White or cream-coloured granules or powder, odourless
2. Identification (IR Spectrum)	Must conform with the Reference Standard Spectrum.
3. pH (1% Solution)	Between 5.0 and 7.0 at 25 degrees C.
4. Loss on Drying	NMT 10.0% at 102 degrees C. for 6 hours.
5. Residue on Ignition	Between 15.0 and 19.0%
6. Protein Content	NMT 0.10%
7. Heavy Metals	NMT 20 ppm (as per USP 23 p. 1727).
8. Arsenic	NMT 2 ppm (as per USP 23, p. 1724).
9. Residual Solvents	a) Acetone: NMT 0.1% b) Ethanol: NMT 2.0% c) Formaldehyde: NMT 100 ppm
10. Sodium Hyaluronate Assay	97.0 to 102.0% (dried basis)
11. Intrinsic Viscosity	Between 10.0 to 14.5 deciliters per gram.
12. Molecular Weight	Between 500,000 to 800,000 daltons
(calculated using the Laurent Formula)	(based on intrinsic viscosity).
13. Total Aerobic Microbial Count	NMT 50 microorganism/gram (as per USP 23, p. 1684).
14. Test for Escherichia coli	Escherichia coli is absent (as per USP 23, p. 1685).
15. Yeasts & Molds	NMT 50 microorganisms/gram (as per USP 23, p. 1686).
16. Endotoxins (LAL)	NMT 0.07 EU/mg (as per USP 23, p. 1696).

A topical grade of hyaluronan may, in certain circumstances be suitable and may be made from the following granules/powder which have the following characteristics:

	<u>Tests</u>	<u>Specifications</u>
	1. Description	White or cream-coloured granules or powder, odourless
5	2. Identification (IR Spectrum)	Must conform to the Reference Standard Spectrum.
	3. pH (1% Solution)	Between 6.0 and 8.0 at 25 degrees C.
10	4. Loss on Drying	NMT 10.0% at 102 degrees C. for 6 hours.
	5. Residue on Ignition	Between 15.0 and 19.0%
	6. Protein Content	NMT 0.40%
	7. Heavy Metals	NMT 20 ppm (as per USP 23 p. 1727).
15	8. Arsenic	NMT 2 ppm (as per USP 23, p. 1724).
	9. Residual Solvents	a) Acetone: NMT 0.1% b) Ethanol: NMT 2.0% c) Formaldehyde: NMT 100 ppm
20	10. Sodium Hyaluronate Assay	97.0 to 102.0% (dried basis)
	11. Intrinsic Viscosity	Between 11.5 to 14.5 deciliters per gram.
25	12. Molecular Weight (calculated using the Laurent Formula)	Between 600,000 to 800,000 daltons (based on intrinsic viscosity).
	13. Total Aerobic Microbial Count	NMT 100 microorganism/gram (as per USP 23, p. 1684).
30	14. Test for Staphylococcus aureus	Staphylococcus aureus is absent (as per USP 23, p. 1684).
	15. Test for Pseudomonas aeruginosa	Pseudomonas aeruginosa is absent (as per USP 23, p. 1684).
	16. Yeasts & Molds	NMT 200 CFU/gram (as per USP 23, p. 1686).
35	This topical grade may then be sterilized.	
	Other forms may be suitable such as one form of hyaluronic acid and/or salts thereof (for example, sodium salt) may be an amount also supplied by Hyal Pharmaceutical Corporation. One such amount is a 15	

ml vial of Sodium hyaluronate 20mg/ml (300mg/vial - Lot 2F3). The sodium hyaluronate fraction is a 2% solution with a mean average molecular weight of about 225,000. The amount also contains water q.s. which is triple distilled and sterile in accordance with the U.S.P. for injection formulations. The vials of hyaluronic acid and/or salts thereof may be carried in a Type 1 borosilicate glass vial closed by a butyl stopper which does not react with contents of the vial.

The amount of hyaluronic acid and/or salts thereof (for example sodium salt) may comprise hyaluronic acid and/or salts thereof having the following characteristics:

- a purified, substantially pyrogen-free fraction of hyaluronic acid obtained from a natural source having at least one characteristic selected from the group consisting of the following:
  - i) a molecular weight within the range of 150,000 - 225,000;
  - ii) less than about 1.25% sulphated mucopolysaccharides on a total weight basis;
  - iii) less than about 0.6% protein on a total weight basis;
  - iv) less than about 150 ppm iron on a total weight basis;
  - v) less than about 15 ppm lead on a total weight basis;
  - vi) less than 0.0025% glucosamine;
  - vii) less than 0.025% glucuronic acid;
  - viii) less than 0.025% N-acetylglucosamine;
  - ix) less than 0.0025% amino acids;
  - x) a UV extinction coefficient at 257 nm of less than about 0.275;
  - xi) a UV extinction coefficient at 280 nm of less than about 0.25; and,
  - xii) a pH within the range of 7.3 - 7.9. Preferably, the hyaluronic acid is mixed with water and the fraction of hyaluronic acid fraction has a mean average molecular weight within the range of 150,000 - 225,000.

Preferably this amount of hyaluronic acid comprises at least one characteristic selected from the group consisting of the following characteristics:



- i) less than about 1% sulphated mucopolysaccharides on a total weight basis;  
 ii) less than about 0.4% protein on a total weight basis;  
 iii) less than about 100 ppm iron on a total weight basis;  
 5 iv) less than about 10 ppm lead on a total weight basis;  
 v) less than 0.00166% glucosamine;  
 vi) less than 0.0166% glucuronic acid;  
 vii) less than 0.016% N-acetylglucosamine;  
 viii) less than 0.00166% amino acids;  
 10 ix) a UV extinction coefficient at 257 nm of less than about 0.23;  
 x) a UV extinction coefficient at 280 nm of less than 0.19; and  
 xi) a pH within the range of 7.5 - 7.7  
 15 Other forms of hyaluronic acid and/or its salts may be chosen from other suppliers, for example those described in prior art documents disclosing forms of hyaluronic acid having lower molecular weights between about 150,000 daltons and 750,000 daltons (protein standard) being prepared as for example, 1-2% solutions in sterile water for intravenous  
 20 administration. In addition, sodium hyaluronate produced and supplied by LifeCore™ Biomedical, Inc. having the following specifications may be suitable (if sterile):

	Characteristics	Specification
25	Appearance	White to cream colored particles
	Odor	No perceptible odor
	Viscosity Average	< 750,000 Daltons
	Molecular Weight	
30	UV/Vis Scan, 190-820nm	Matches reference scan
	OD, 260nm	< 0.25 OD units
	Hyaluronidase Sensitivity	Positive Response
	IR Scan	Matches reference
	pH, 10mg/g solution	6.2 - 7.8
35	Water	8% maximum
	Protein	< 0.3 mcg/mg NaHy
	Acetate	< 10.0 mcg/mg NaHy
	Heavy Metals, maximum ppm	

	As	Cd	Cr	Co	Cu	Fe	Pb	Hg	Ni
	2.0	5.0	5.0	10.0	10.0	25.0	10.0	10.0	5.0
	Microbial Bioburden					None observed			
	Endotoxin					< 0.07EU/mg NaHy			
5	Biological Safety Testing					Passes Rabbit Ocular			
						Toxicity Test			

The following references teach hyaluronic acid, sources thereof and processes of the manufacture and recovery thereof.

Canadian Letters Patent 1,205,031 (which refers to United States  
 10 Patent 4,141,973 as prior art) refers to hyaluronic acid fractions having average molecular weights of from 50,000 to 100,000; 250,000 to 350,000; and 500,000 to 730,000 and discusses processes of their manufacture

Where high molecular weight hyaluronic acid (or salts or other  
 15 forms thereof) is used, it must, prior to use be diluted to permit administration and ensure no intramuscular coagulation. Recently, it has been found that large molecular weight hyaluronic acid having a molecular weight exceeding about 1,000,000 daltons self-aggregates and thus, does not interact very well with HA receptors. Thus, the larger molecular weight hyaluronic acid (such as Healon™) should be avoided.

20 Thus, according to an aspect of the invention, the invention provides a composition comprising a therapeutically effective amount of paclitaxel with a therapeutically effective amount of hyaluronic acid and/or a pharmaceutically acceptable salt thereof, together with a pharmaceutically-acceptable diluent wherein the therapeutically effective  
 25 amount of paclitaxel is at a significantly reduced level than would be normally used (for example greater than three times less). Thus the amount of paclitaxel reduced from that normally used, is "spared".

The invention also provides a method of treatment of a pathological condition in a subject in need of such treatment, comprising  
 30 the step of administering an effective dose of a composition according to the invention to said subject over such period as may be required. For example, the treatment may continue for months. However in each instance the effective amount of the agent is "spared".

The invention also provides the use of a composition comprising a  
 35 form of hyaluronan and an effective dosage amount of paclitaxel for treating a pathological condition (cancer) and wherein the therapeutically effective amount of paclitaxel is at a significantly reduced level than would be normally used (for example greater than three times less).

It will be clearly understood that the dose and route of administration will depend upon the condition to be treated, and the attending physician will readily be able to determine suitable doses and routes.

5           The subject to be treated may be a human (or may be an animal).

          The invention further provides a method of preparing a composition of the invention, comprising the step of combining such highly lipophilic therapeutic compound paclitaxel with hyaluronan and/or a pharmaceutically-acceptable salt thereof, and a diluent (such as  
10       sterile water) and put into a suitable pharmaceutically acceptable tolerable form (which is of course, non-toxic). The agent once again will be "spared". The inventors believe that the unique attraction between hydrophobic patches of the hyaluronan and paclitaxel enable the paclitaxel to be "spared".

15           While hyaluronan (HA) is generally hydrophilic, it has these hydrophobic patches which Applicants believe permit the binding/association of the hyaluronan with the paclitaxel. These hydrophobic patches are dispersed on the molecule. Because of the dispersion and lack of knowledge of the exact positions, it is not known if  
20       any particular compound combined with the hyaluronan would be capable of being spared to provide effective dosages to the patient.

          The invention will now be illustrated with reference to the following tests which illustrate the invention.

          The tumour model used in the tests was that described in detail on  
25       pages 59 - 60 of Fourth International Workshop - on Hyaluronan in Drug Delivery as follows:

Colon-26 cells

          Colon-26 cells, a gift from the Imperial Cancer Research Fund (London), were maintained in antibiotic  
30       supplemented DMEM containing 10% fetal calf serum at 37°C in 95% oxygen/5% carbon dioxide.

Tumour Induction

          Anaesthetized BALB/c mice were subcutaneously implanted with sponges (8 x 4 mm) and seeded with 10<sup>6</sup>  
35       Colon-26 cells three days later by injection.

          The tumours were allowed to establish for 4 days before dosing was initiated. Dosing was intravenous (0.25ml/day) for 6 days of amounts as shown in the table below and the tumours were excised 24 hours after the

last dose. The data so far relates to wet and dry weights of the tumour mass, and is shown in the following table:

Group	n	Wet Weight/mg	Dry Weight/mg
Control PBS	7	470 ± 15	84.5 ± 4.2
Cremophor	9	514 ± 39	94.4 ± 7.8
Taxol 2.5mg/kg	6	482 ± 37	81.7 ± 9.2
Taxol 10mg/kg	8	464 ± 30	73.9 ± 6.4*
HA 7.5mg/kg	7	485 ± 28	72.1 ± 5.3*
Taxol 2.5mg/kg + HA 7.5mg/kg	8	391 ± 38*	60.4 ± 8.0**

\* p<0.05

\*\* p<0.01 comparison with Cremophor control.

- 5 HA = hyaluronan (sodium hyaluronate (EM) having a molecular weight between 50,000 and 750,000 daltons (protein standard)

10 Taxol was solubilised in a mixture of 1:1 ethanol and cremophor EL. Further dilution was in sterile PBS. The final cremophor concentration in all Taxol groups was 1.6%. A similar solution served as vehicle control (the cremophor group in the table above). The HA alone should be compared with the PBS control group. Numbers refer to dose in mg/kg.

The dry weights are of particular interest. We have a dose response reduction in dry weight with Taxol, and the combination of low dose Taxol with HA gives the greatest suppression of all.

- 15 To note: the reduction in tumour weight caused by HA alone; this is significant only against the Cremophor and not the PBS control. Nonetheless, the data speaks for itself and demonstrates that HA had no detrimental effect on tumour growth. In fact it appears to suppress tumour growth possibly to the same extent as the high dose Taxol. (See  
20 PCT application WO 95/30423). The form of HA and Taxol™ may be administered in any suitable manner such as by direct injection, intravenous administration etc.

- 25 As many changes can be made to the embodiments without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A dosage amount of a pharmaceutical composition, the dosage amount comprising an effective amount of a form of hyaluronan selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof having a molecular weight less than 750,000 daltons (Protein Standard), suitable excipients for administration and an effective amount of paclitaxel which is less than the usual dosage amount of the medicine when administered alone in suitable excipients.
2. The dosage amount of the pharmaceutical composition of claim 1 wherein the amount of medicine in the dosage amount is at least about 3 times less than the usual dosage amount administered for treatment.
3. The dosage amount of claim 2 wherein the molecular weight of hyaluronan is greater than 150,000 daltons.
4. A method of treating a patient suffering a disease or condition comprising administering a dosage amount according to claim 1, 2 or 3 to the patient for such period of time as required.
5. The use of hyaluronan and a lesser amount of taxol than is normally used to treat a disease in the manufacture of a dosage amount of a pharmaceutical composition wherein the dosage amount comprises an effective amount of each of, a form of hyaluronan selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof having a molecular weight less than 750,000 daltons (Protein Standard), suitable excipients for administration and paclitaxel which is present in the dosage amount in an amount less than the usual dosage amount of the medicine when administered alone.
6. The use of claim 5 wherein the amount of the paclitaxel in the dosage amount is at least about 3 times less than the usual dosage amount administered during treatment.

7. The use of claim 5 or 6 wherein the molecular weight of the form of hyaluronan exceeds about 150,000 daltons.
8. The use of hyaluronan having a molecular weight less than 750,000 daltons (protein standard) and an amount of paclitaxel less than the amount of paclitaxel normally used to treat pathological tissue which expresses excess hyaluronan receptors.
9. The use of claim 8 wherein the amount of the paclitaxel in the dosage amount is at least about 3 times less than the usual dosage amount administered during treatment.
10. The use of claim 8 or 9 wherein the molecular weight of the form of hyaluronan exceeds about 150,000 daltons.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CA 98/00660

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K31/335 A61K47/36

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 25020 A (PHARMACIA AB ; MAANSSON PER (SE); ROLFSEN WENCHE (SE); WICKSTROEM K) 10 November 1994 * p.4, 1st full par. & 2nd full par., last sen.; claims 1-5 *	1-10
A	WO 90 09401 A (PHARMACIA AB) 23 August 1990 * p.4, last sent.-p.5, 1st par. *	1-10
Y	WO 95 30423 A (NORPHARMCO INC ; FALK RUDOLF EDGAR (CA); ASCULAI SAMUEL SIMON (CA)) 16 November 1995 cited in the application see the whole document -/--	1-10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

15 October 1998

Date of mailing of the international search report

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# INTERNATIONAL SEARCH REPORT

Int. l. Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KLEIN ET AL : "Effects of hyaluronic acid on experimental tumor uptake of 5-fluorouracil" REG CANCER TREAT, vol. 7, 1994, pages 163-4, XP002080735 see the whole document ---	1-10
A	WO 93 24476 A (CLOVER CONS LTD ;SOON SHIONG PATRICK (US); DESAI NEIL P (US); SAND) 9 December 1993 see claims 1,23 -----	1-10



# INTERNATIONAL SEARCH REPORT

Information on patent family members

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